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VARIANINC LEGAL DEPT

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Docket No.: 03-41US  
Serial No. 10/788,592

**REMARKS**

This submission is in response to the Office Action, dated November 15, 2007, a response to which is due on February 15, 2008. As this submission is timely submitted and no additional excess claims fees are due, there are no fees due.

Favorable consideration is respectfully requested in view of the foregoing Amendments and following Remarks.

**I. STATUS OF THE CLAIMS:**

Applicants appreciate the Examiner's withdrawal of the previous anticipation rejections of claims 1-24, and the indication of allowability of claims 47 and 51.

In the reply dated September 7, 2007, claims 3, 7-8, 21, and 25-45 were canceled without prejudice. Applicants expressly reserve their right under 35 U.S.C. § 121 to file a divisional application directed to the nonelected subject matter during the pendency of this application.

Claims 1 and 20 have been amended to delete the term "silicone oil". Claims 47 and 51 have been amended to independent form as suggested by the Examiner, and are now allowable over the art of record.

New claims 52-53 have been added. Claim 52 finds support in original claims 20 and 21, and in the Specification on page 25, line 10- page 27, line 30 (Examples 3 and 4). Claim 53 finds support in original claim 9, and in the Specification at page 11, section II.A.2.

With respect to new claims 52 and 53, Applicants respectfully submit that these claims are patentable over the art cited by the Examiner. In particular, there is no teaching or suggestion to utilize liquid membranes comprising a *mixture* comprising a silicone oil and a fatty acid ester, a vegetable oil, or a nitroarylalkylether in liquid phase microextraction, or that such membranes would be stable for long periods of time.

Accordingly, upon entry of this amendment, claims 1, 2, 4-6, 9-20, 22-24, and 46-53 are pending and under examination. No new matter has been introduced by way of these amendments.

**II. WITHDRAWN REJECTIONS AND ALLOWABLE SUBJECT MATTER**

Applicant appreciates the withdrawal of the rejections of claims 1-24 in view of the

**Docket No.: 03-41US  
Serial No. 10/788,592**

arguments presented in the response dated September 7, 2007. Applicant further appreciates the Examiner's indication that a hollow fiber liquid membrane on a porous polymeric substrate with a preservative in the use of liquid extraction is not found in the prior art, and that claims 47 and 51 would be allowable if rewritten in independent form.

**III. REJECTIONS UNDER 35 U.S.C. § 103(a) OVER WO 02/0088672 IN VIEW OF U.S.**

**PATENT No. 5,507,949**

Claims 1-2, 9-10, 13-20, 22-24, 46 and 50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 02/0088672 (herein referred "Varian, Inc.", and further in view of U.S. Patent No. 5,507,949 to Ho (herein referred "Ho").

Regarding claim 1, the Examiner alleged that Varian, Inc. discloses a device for performing clean-up and enrichment of analytes of interest, wherein a donor sample comprising an analyte of interest is inserted into a tubular hollow porous fiber into a well, where the hollow fiber comprises of a liquid extraction membrane. The Examiner stated that the hollow fiber enclosing an internal cavity is separated from the donor sample by the extraction membrane, a static acceptor liquid is placed in the internal cavity, and the analyte of interest is enriched by extracting the analyte of interest from the donor through the extraction membrane into the acceptor liquid in the internal cavity. The analyte of interest is transferred and the acceptor liquid from the internal cavity is transferred to the analysis device (see page 1, line 29 - page 2, line 5). The Examiner conceded that Varian, Inc. does not disclose a membrane comprising a support comprising a fatty acid ester, a vegetable oil or silicon oil. The Examiner alleged that Ho discloses an immobilized liquid membrane for selective extraction where the membrane comprises a polymeric liquid supported or immobilized within a microporous support, which may be hydrophobic, and stated that "it is known in the art that a media for removing halogenated hydrocarbons from aqueous streams may be in contact with a microporous polyolefin film impregnated with silicone oil, vegetable oil and animal fats and waxes." The Examiner pointed out an example where an immobilized liquid membrane was prepared in a cell, silicone oil was used as the liquid membrane (citing the abstract, column 2, lines 13-21, column 14, lines 11-12). Further, the Examiner alleged that it would have been obvious to one having ordinary skill in the art at the time the invention was made to use silicon oil as the liquid membrane to enhance separation and isolation of the analyte of interest.

Docket No.: 03-41US  
Serial No. 10/788,592

In response, Applicants respectfully traverse these rejections. First of all, claim 1 has been amended to delete silicone oil as a constituent. In addition, the Examiner's statement that "it is known in the art that a media for removing halogenated hydrocarbons from aqueous streams may be in contact with a microporous polyolefin film impregnated with silicone oil, vegetable oil and animal fats and waxes" is misplaced and irrelevant, in that the passage cites U.S. Patent No. 4,276,179 as purportedly disclosing "a process for *removing by adsorption*." Adsorption is not the same process as liquid phase microextraction as instantly claimed, and thus teaches a different process than what is claimed. Accordingly, the portion of Ho cited by the Examiner *teaches away* from use of silicone oil as a liquid membrane substituent for liquid phase extraction, instead teaching its suitability for solid phase extraction, a completely different application. However, the claim limitation has now been deleted, therefore the rejection is now moot, and Applicants respectfully submit that the rejection be withdrawn.

Regarding claim 2, the Examiner stated that Varian, Inc. and Ho disclose the claimed invention in that Varian, Inc. discloses that the membrane used in the invention can be produced in many forms such as a hollow fiber (see page 6, lines 9-10).

In response, as claim 1 (from which claim 2 depends) has been amended and is patentable over the art cited, Applicants respectfully submit that the rejection has been overcome and request that the rejection be withdrawn.

Regarding claim 9, the Examiner stated that Varian, Inc. and Ho disclose the claimed invention in that Varian, Inc. discloses that the microporous semi-permeable membrane permits selective filtration according to the size of the micropores. The Examiner alleged that the molecular weight cutoff of the membrane allows passage of small molecules such as drugs while precluding passage of large molecules such as proteins. The Examiner further alleged that the porous electrically charged or ion-exchange membranes have a pore wall with fixed positive or negative charges, the passage of ionic molecules across the membrane is governed by pore size and membrane charge, and that the analytes of interest pass through the membrane into the acceptor solution, leaving interferences in the donor solution (see page 6, lines 12-22).

In response, as claim 1 (from which claim 9 depends) has been amended and is patentable over the cited art, Applicants respectfully submit that the rejection has been overcome and request that the rejection be withdrawn. In addition, the passage of Varian Inc. cited by the Examiner does not relate to the use of a carrier, as recited by claim 9.

Docket No.: 03-41US  
Serial No. 10/788,592

Regarding claim 10, the Examiner stated that Varian, Inc. and Ho disclose the claimed invention in that Varian, Inc. discloses supported liquid membranes where the pH of the donor solution is adjusted below the pKa value of the acid, the ionization of the carboxylic acid is suppressed and the nonionic form to be extracted is allowed to form in the immobilized liquid membrane. Polymeric membranes are also formed by the polymerization of monomers in the pores of the support material (see page 7, lines 8- 11, page 8, lines 30-31).

In response, as claim 1 (from which claim 10 depends) has been amended and is patentable over the cited art, Applicants respectfully submit that the rejection has been overcome and request that the rejection be withdrawn. In addition, as the present application and pending claims relate to liquid membranes supported by a porous polymeric substrate, but not to polymeric membranes, the mention of polymeric membranes by Varian, Inc. is not relevant to patentability.

Regarding claims 13-15, the Examiner stated that Varian, Inc. and Ho disclose the claimed invention in that Varian, Inc. discloses the polymeric membrane from the polymerization of monomers in the pores of the support materials which can be a polymer such as polyethylene glycols, polyvinylpyrrolidones, polyesters, polyurethanes and functionalized polyolefins. The Examiner stated that the fibers in the well plates may also be modified by several permutations and combinations of parameters to incorporate selectivity features, which would permit the isolation of a single analyte from a complex mixture. The fibers can be made from different polymeric materials such as polypropylene, polysulfone, polycarbonate or polyester sulfate (see page 8, line 30-page 9, line 1, page 10, lines 13-18).

In response, as claim 1 (from which claims 13-15 depend) has been amended and is patentable over the cited art, Applicants respectfully submit that the rejection has been overcome and request that the rejection be withdrawn. In addition, as the present application and pending claims relate to liquid membranes supported by a porous polymeric substrate, but not to polymeric membranes, the mention of polymeric membranes by Varian, Inc. is not relevant to patentability.

Regarding claim 16-17, the Examiner stated that Varian, Inc. and Ho disclose the claimed invention in that Varian, Inc. does not disclose the liquid membrane is stable for at least 30, 60 or 90 days and where the hollow fiber is able to extract at least one analyte after being stored for at least 30, 60 or 90 days. The Examiner further stated that Ho discloses that

Docket No.: 03-41US  
Serial No. 10/788,592

the stable supported liquid membrane can be handled and stored for months at room temperature air due to the practically nonvolatile nature of PPG, and that the microporous polypropylene membrane wet with polypropylene glycol and the same wetting procedure can be used for hollow fiber membrane (see column 11, lines 1-13). The Examiner stated that since the supported liquid membrane and the hollow fiber are made by the same wetting technique, the time frame for the storage of the membrane is the same. The Examiner further stated that the storage time of months can be up to 90 days or more, and it would have been obvious to one having ordinary skill in the art at the time the invention was made to preserve the hollow fiber liquid membrane for months at a time so that one can make many hollow fiber membranes at one time and store the remaining membranes for future use while not worrying about the integrity of the membrane separation capabilities.

In response, as claim 1 (from which claims 16-17 depend) has been amended and is patentable over the cited art, Applicants respectfully submit that the rejection has been overcome and request that the rejection be withdrawn. In addition, the standard of *In re Boesch* with regard to discovering an optimum value for a variable applies only to variables that a person of ordinary skill in the art can actually vary in routine experiments. The observed experimental results regarding duration of usability of liquid membranes represents *output* parameters from the experiments (what is observed) and not *input* variables (what is varied) that can be routinely adjusted. Achieving a particular experimental *output* or result can occasionally be obvious if prior art shows a known functional relationship between the output and input variables, but if, as in this case, no such known functional relationship exists, then the required experiments are not at all routine. See *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) and MPEP § 2144.05.II.B: "*A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation.*" [Emphasis added]. The "particular parameter" in the present invention is the number of days for which the liquid membrane is stable. This parameter is not a "result-effective variable," in that prior art has not achieved a recognized result in correlating the choice of liquid membrane materials with this variable, and more than routine experimentation is required to find materials which can be used to make liquid membranes with the claimed stability.

Docket No.: 03-41US  
Serial No. 10/788,592

Further, the disclosure by Ho of allegedly stable liquid membranes prepared using silicone oil is not predictive of the success of Applicants' liquid membranes comprising vegetable oil or fatty acid esters, or mixtures thereof. Accordingly, one skilled in the art at the time the invention was made *would not have had a reasonable expectation of success* that liquid membranes could be formed from vegetable oil and fatty acid esters, and that the liquid membranes so formed would be stable for at least 30, 60 or 90 days. Therefore, for all of the aforementioned reasons, Applicants respectfully submit that this rejection has been overcome and should be withdrawn.

Regarding claim 18, the Examiner stated that Varian, Inc. and Ho disclose the claimed invention because Varian, Inc. discloses a two-phase extraction system where an aqueous feed solution is on the shell side of the fiber and organic solvent acceptor solution is on the lumen side with the same solvent forming the supported membrane (see page 12, lines 1-3).

In response, as claim 1 (from which claim 18 depends) has been amended and is patentable over the cited art, Applicants respectfully submit that the rejection has been overcome and request that the rejection be withdrawn. In addition, as the present application and pending claims do not relate two-phase extraction systems, mention of an organic solvent acceptor by Varian, Inc. is not relevant to patentability of claim 18.

Regarding claim 19, the Examiner stated that Varian, Inc. and Ho disclose the claimed invention because Varian, Inc. discloses that "simple supported liquid membrane hollow fiber devices can be employed in the well plate and an autosample vial formats in a static [sic, static] mode can furnish a high degree of sample enrichment" (see page 11, lines 30-32).

In response, as claim 1 (from which claim 19 depends) has been amended and is patentable over the cited art, Applicants respectfully submit that the rejection has been overcome and request that the rejection be withdrawn.

Regarding claim 20, the Examiner stated that Varian, Inc. discloses a device for performing clean-up and enrichment of analytes of interest where a donor sample comprising of an analyte of interest is inserted into a tubular hollow porous fiber into a well, and where the hollow fiber comprises a liquid extraction membrane. The Examiner stated that a hollow fiber encloses an internal cavity separated from the donor sample by the extraction membrane and a static acceptor liquid is placed in the internal cavity, and enrichment of the analyte of interest is done by extracting the analyte of interest from the donor through the extraction membrane into the acceptor liquid in the internal cavity, and the analyte of interest is

Docket No.: 03-41US  
Serial No. 10/788,592

transferred and the acceptor liquid is transferred from the internal cavity to the analysis device (see page 1, line 29 - page 2, line 5). The Examiner conceded that Varian, Inc. does not disclose the membrane comprising a support comprising a fatty acid ester, a vegetable oil or a silicone oil. However, the Examiner further stated that Ho discloses an immobilized liquid membrane for the selective extraction where the membrane comprises "a polymeric liquid support or immobilized within a microporous support, which may be hydrophobic." The Examiner alleged that it is known in the art that a media for removing halogenated hydrocarbons from aqueous streams may be in contact with a microporous polyolefin film impregnated with silicone oil, vegetable oil and animal fats and waxes, and pointed to an example where an immobilized liquid membrane is prepared in a cell, and silicone oil was used as the liquid membrane (see Ho abstract and column 2, lines 13-21, column 14, lines 11-12). The Examiner stated that it would have been obvious to one having ordinary skill in the art at the time the invention was made to use silicone oil as the liquid membrane to enhance separation and isolation of the analyte of interest.

In response, Applicants respectfully traverse these rejections. First of all, claim 20 has been amended to delete silicone oil as a constituent. In addition, the Examiner's statement that "it is known in the art that a media for removing halogenated hydrocarbons from aqueous streams may be in contact with a microporous polyolefin film impregnated with silicone oil, vegetable oil and animal fats and waxes" is misplaced and irrelevant, in that the passage cites U.S. Patent No. 4,276,179 as purportedly disclosing "a process for *removing by adsorption*." Adsorption is not the same process as liquid phase microextraction as instantly claimed, and thus teaches a different process than what is claimed. A teaching of adsorption is, in fact, a *teaching away* from suitability for liquid phase microextraction, in that adsorption implies that the analyte adsorbs to the oil and would not be able to pass through the liquid membrane to the acceptor solution. Accordingly, the portion of Ho cited by the Examiner *teaches away* from use of silicone oil as a liquid membrane substituent for liquid phase extraction, instead teaching its suitability for solid phase extraction, a completely different application. However, the claim limitation has now been deleted, therefore the rejection is now moot. Accordingly, Applicants respectfully submit that the rejection be withdrawn.

Regarding claims 22-23, the Examiner stated that Varian, Inc. and Ho disclose the claimed invention because Varian, Inc. discloses the polymeric membrane is formed from the polymerization of monomers in the pores of the support materials which can be a polymer

**Docket No.: 03-41US  
Serial No. 10/788,592**

such as polyethylene glycols, polyvinylpyrrolidones, polyesters, polyurethanes and functionalized polyolefins, and that the fibers in the well plates may also be modified by several permutations and combinations of parameters to incorporate selectivity features, which would permit the isolation of a single analyte from a complex mixture. The Examiner stated that the fibers can be made from different polymeric materials such as polypropylene, polysulfone, polycarbonate or polyester sulfate (see page 8, line 30-page 9, line 1, page 10, lines 13-18).

In response, as claim 20 (from which claims 22-23 depend) has been amended and is patentable over the cited art, Applicants respectfully submit that the rejection has been overcome and request that the rejection be withdrawn. In addition, as the present application and pending claims relate to liquid membranes supported by a porous polymeric substrate, but not to polymeric membranes, the mention of polymeric membranes by Varian, Inc. is not relevant to patentability.

Regarding claim 24, the Examiner stated that Varian, Inc. and Ho disclose the claimed invention because Varian, Inc. does not disclose that the liquid membrane is stable for at least 30, 60 or 90 days, however, Ho discloses the stable supported liquid membrane can be handled and stored for months at room temperature air due to the practically nonvolatile nature of PPG, and the microporous polypropylene membrane wet with polypropylene glycol and the same wetting procedure can be used for hollow fiber membrane (see column 11, lines 1-13). The Examiner stated that the storage time of months can be up to 90 days or even more, and it would have been obvious to one having ordinary skill in the art at the time the invention was made to store and preserve the liquid membrane for months at a time keep a stock of liquid membranes so one does not need to make membranes every time separation of analytes needs to occur.

In response, as claim 20 (from which claim 24 depends) has been amended and is patentable over the cited art, Applicants respectfully submit that the rejection has been overcome and request that the rejection be withdrawn. In addition, the Examiner errs in citing the stability of PPG films taught by Ho in that PPG films are not made of fatty acid esters or vegetable oil as required by claim 20. With regard to the possibility that such stability might otherwise be obvious by virtue of need to one skilled in the art, Applicant again refers the Examiner to the standard of *In re Boesch* wherein discovering an optimum value for a variable applies only to variables that a person of ordinary skill in the art can

Docket No.: 03-41US  
Serial No. 10/788,592

actually vary in routine experiments. The observed experimental results regarding duration of usability of liquid membranes represents *output* parameters from the experiments (what is observed) and not *input* variables (what is varied) that can be routinely adjusted. Achieving a particular experimental *output* or result can occasionally be obvious if prior art shows a known functional relationship between the output and input variables, but if, as in this case, no such known functional relationship exists, then the required experiments are not at all routine. See *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) and MPEP § 2144.05.II.B: "*A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation.*" [Emphasis added]. The "particular parameter" in the present invention is the number of days for which the liquid membrane is stable. This parameter is not a "result-effective variable," in that prior art has not achieved a recognized result in correlating the choice of liquid membrane materials with this variable, and more than routine experimentation is required to find materials which can be used to make liquid membranes with the claimed stability.

Further, the disclosure by Ho of allegedly stable liquid membranes prepared using silicone oil is not predictive of the success of Applicants' liquid membranes comprising vegetable oil or fatty acid esters, or mixtures thereof. Accordingly, one skilled in the art at the time the invention was made *would not have had a reasonable expectation of success* that liquid membranes could be formed from vegetable oil and fatty acid esters, and that the liquid membranes so formed would be stable for at least 30, 60 or 90 days.

Therefore, for all of the aforementioned reasons, Applicants respectfully submit that this rejection has been overcome and should be withdrawn.

Regarding claim 46, the Examiner stated that Varian, Inc. and Ho disclose the claimed invention because Varian, Inc. discloses a membrane was formed with small molecular weight organic liquids that comprised an aryl alkyl ether containing the polar nitro functionality (see page 34, lines 23-26).

In response, as claim 1 (from which claim 46 depends) has been amended and is patentable over the cited art, Applicants respectfully submit that the rejection has been overcome. In addition, Applicants respectfully submit that there is no suggestion, motivation or teaching in the cited references or the art to provide a device comprising a porous

**Docket No.: 03-41US  
Serial No. 10/788,592**

polymeric substrate with a liquid membrane supported thereon, wherein the liquid membrane comprises a fatty acid ester, or a vegetable oil, or mixtures thereof, and further comprising a nitroarylalkylether. Applicants thus respectfully submit that this rejection has been overcome and should be withdrawn.

Regarding claim 50, the Examiner stated that Varian, Inc. and Ho disclose the claimed invention because Varian, Inc. discloses a membrane was formed with small molecular weight organic liquids that comprised an aryl alkyl ether containing the polar nitro functionality (see page 34, lines 23-26).

In response, as claim 20 (from which claim 50 depends) has been amended and is patentable over the cited art, Applicants respectfully submit that the rejection has been overcome. In addition, Applicants respectfully submit that there is no suggestion, motivation or teaching in the cited references or the art to provide a device comprising a porous polymeric substrate with a liquid membrane supported thereon, wherein the liquid membrane comprises a fatty acid ester, or a vegetable oil, or mixtures thereof, and further comprising a nitroarylalkylether.

Applicants thus respectfully submit that the rejections of claims 1-2, 9-10, 13-20, 22-24, 46 and 50 under 35 U.S.C. § 103(a) over Varian, Inc. and further in view of Ho have been overcome and should be withdrawn.

**IV. REJECTIONS UNDER 35 U.S.C. § 103(a) OVER WO 02/0088672 AND U.S. PATENT NO. 5,507,949 AND FURTHER IN VIEW OF U.S. PATENT NO. 3,959,173**

Claims 4-5 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Varian, Inc. and Ho as applied to claim 1 above, and further in view of U.S. Patent No. 3,959,173 to Li (hereinafter "Li"). The Examiner stated that Varian, Inc. and Ho disclose the claimed invention except for where the fatty acid ester comprises an acyl chain comprising from 12 to 30 carbon atoms. The Examiner further stated that Li discloses a liquid membrane based off of the formulation of emulsions, where emulsions are used for the separation of dissolved components from aqueous solutions, and that the emulsion of the liquid membrane comprises an oil-soluble surfactant, which can include an nonionic surfactant. The Examiner stated that the most preferred nonionic surfactant is Span 80 TM from Atlas Chemical, a fatty acid ester of anhydrosorbitol (see abstract, column 3, lines 62-66, column 4, lines 30-32), and that it is known in the art that Span 80 TM has an acyl chain of 18 carbons and an ester portion of 8

Docket No.: 03-41US  
Serial No. 10/788,592

carbons. The Examiner alleged that it would have been obvious to one having ordinary skill in the art at the time the invention was made to have the membrane be made of a fatty acid ester with an acyl chain from 12 to 30 carbon atoms so that membrane is resistant to cleavage of donor or acceptor solutions in the well and may sustain multiple uses.

In response, as claim 1 (from which claims 4-5 depend) has been amended and is patentable over the cited art, Applicants respectfully submit that the rejection has been overcome. In addition, the feature of claim 5 that the "fatty acid ester comprises an ester portion comprising from 1 to 12 carbon atoms" is clearly not satisfied by the surfactant described by Li because Span 80 has anhydrosorbitol in the ester portion, which is a cyclic moiety and is not included in the class of fatty acid esters as defined in the Specification ("The fatty acid esters may be saturated, unsaturated, linear or branched...". See page 10, line 16-18). Further, Li's Span 80 is a surfactant, not a fatty acid ester as used herein and as recited in claims 4-5. One skilled in the art would understand that a fatty acid ester of anhydrosorbitol would not function to form a liquid membrane as recited in claims 1, 4 and 5, and to the contrary, use of a surfactant as taught by Li would *destroy* the liquid membrane by causing the constituents of the liquid membrane to form an emulsion in the aqueous medium, rather than remaining intact and stable on the surface of the porous polymeric substrate. In fact, Li's use of a surfactant serves to *teach away* from the present claims because if one skilled in the art were to attempt to prepare liquid membranes using a surfactant such as the fatty acid ester of anhydrosorbitol, only an emulsion of surfactant would result, and no liquid membrane would be formed at all.

Applicants thus respectfully submit that the rejection of claims 4-5 over Varian, Inc. and Ho as applied to claim 1 above, and further in view of Li, has been overcome and should be withdrawn.

**V. REJECTIONS UNDER 35 U.S.C. § 103(a) OVER WO 02/0088672 AND U.S. PATENT NO. 5,507,949 AND FURTHER IN VIEW OF U.S. PATENT NO. 5,603,953**

Claim 6 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Varian, Inc. and Ho as applied to claim 1 above, and further in view of U.S. Patent No. 5,603,953 to Herbig et al (hereinafter "Herbig"). The Examiner stated that Varian, Inc. and Ho disclose the claimed invention except for where the vegetable oil is soya oil, olive oil or teatree oil. The Examiner further stated that "Herbig discloses a supported liquid membrane delivery

Docket No.: 03-41US  
Serial No. 10/788,592

device that releases a beneficial agent to an aqueous environment used in solvent extraction. The device in the invention included a polyvinylidenefluoride or polyalkene porous membrane with a triglyceride entrained therein. Preferred within the group are devices where the hydrophobic liquid membrane is triolein or olive oil. In an example using the device, a supported liquid membrane was produced by filling the pores of a disk of Accurel A3 polypropylene membrane with olive oil" (see abstract, column 3, line 30-33, column 12, line 66-column 13, line 2, column 15, lines 40-44). The Examiner stated that it would have been obvious to one having ordinary skill in the art at the time the invention was made to have the liquid membrane be of a vegetable oil so that beneficial agent are released when in used in the extraction of a solvent.

In response, Applicants respectfully traverse this rejection. Herbig purports to disclose drug delivery devices, comprising a microporous hydrophobic support membrane that at least partially surrounds a beneficial agent-containing hydrophilic formulation, that release a beneficial agent to an aqueous environment following exposure to an environmental trigger. A hydrophobic liquid is allegedly held within the microporous support and is substantially impermeable to the aqueous environment, and the hydrophilic formulation is subsequently released upon exposure to an environmental trigger such as an enzyme. See Abstract and Summary of the Invention. Herbig further states that the devices function as a result of the interaction of an environmental trigger that results in a decrease in the hydrophobicity of the hydrophobic liquid, allowing subsequent transport of an aqueous environmental medium through the porous membrane and subsequent release of beneficial agent, wherein the release can occur by simple diffusion, osmotic pumping or osmotic bursting. See Col. 4, lines 55- 66. The trigger means is described as including enzymes, nucleophiles, reducing agents, oxidizing agents, heat and light. See Col. 5, lines 9-14. In addition, Herbig states at Col. 5, lines 17-39:

Any hydrophobic liquid (hydrophobic liquid means) may be used that inhibits release of the beneficial agent and is responsive to the environmental trigger. The hydrophobic liquid should be capable of transformation such that it becomes permeable to the aqueous environment or the beneficial agent containing the hydrophilic formulation. The interaction between the support membrane, hydrophobic liquid and aqueous solution should change in response to the trigger, to allow aqueous flux through the pores of the membrane. ... The transformation increases the hydrophilicity of the liquid thus increasing the permeability of water by lowering the interfacial tension between the support membrane and water or the liquid and water. This allows

Docket No.: 03-41US  
Serial No. 10/788,592

the beneficial agent to be released, either by diffusion or by some other mechanism initiated by entering water (such as osmotic bursting).

In other words, Herbig teaches that the hydrophobic liquid (in this case triolein or olive oil) used in his device *should inhibit release* of the beneficial agent until triggered by a desired environmental trigger. This teaching is in direct contradiction to the requirements of the device for performing liquid phase microextraction of the pending claims, in that the liquid membrane of the instant claims is required to allow passage of the analyte to be extracted from the sample solution and accumulated into the acceptor solution, in order for liquid phase microextraction to occur. In fact, Herbig *teaches away* from the present claim 6 because it suggests that if one skilled in the art were to use a vegetable oil such as soya oil, olive oil or tea tree oil to perform liquid phase microextraction, no extraction of analytes would be performed at all because Herbig teaches that the oil is impermeable to analytes until increased permeability is triggered. Example 1 cited by the Examiner describes experiments with olive oil and demonstrates that increased permeability was not observed until triggered by pancreatic lipase, i.e., Herbig teaches that the liquid membrane was not permeable until triggered. Therefore, one having ordinary skill in the art at the time the invention was made *would not have had a reasonable expectation of success* or been motivated to form a liquid membrane of a vegetable oil so that beneficial agent could be released or so that analytes could be extracted by liquid phase microextraction.

Further, the Examiner errs in stating that the use of the vegetable oils recited in claim 6 would have been obvious when used in the extraction of a solvent, because the instant claims do not involve solvent extraction, and the devices and methods disclosed in the present Specification and claims would in fact be rendered inoperative if solvent extraction methods were implemented with the devices. Further, the instant claims do not relate to the release of beneficial agent, a process utilizing a concentration gradient, but instead relate to the extraction of analytes from a sample, a process which can *create* a concentration gradient. One having ordinary skill in the art would not be taught, suggested or motivated by Herbig to perform liquid phase microextraction using vegetable oils of claim 6, since Herbig states that the liquid membrane *should inhibit release* of the beneficial agent, i.e., Herbig implies that *liquid membranes formed from olive oil are not permeable to analytes sought to be extracted*. Accordingly, there is *no reasonable expectation of success* in practicing the claimed invention based on the teachings of Herbig.

**Docket No.: 03-41US  
Serial No. 10/788,592**

Thus, for these additional reasons, Applicants respectfully submit that Herbig does not teach, suggest or motivate one skilled in the art to use a vegetable oil such as soya oil, olive oil or tea tree oil in the claimed devices and methods. Applicants thus respectfully submit that the rejection of claim 6 over Varian, Inc. and Ho as applied to claim 1 above, and further in view of Herbig, has been overcome and should be withdrawn.

**VI. REJECTIONS UNDER 35 U.S.C. § 103(a) OVER WO 02/0088672 AND U.S. PATENT NO. 5,507,949 AND FURTHER IN VIEW OF JOHNSSON**

Claim 12 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Varian, Inc. and Ho as applied to claim 1 above, and further in view of Jonsson et al (hereinafter referred "Jonsson"). The Examiner stated that Varian, Inc. and Ho disclose the claimed invention except for where the carrier is an organic ion selected from the list presented in the claim. The Examiner stated that Jonsson discloses that membranes used in the extraction in analytical chemistry in sample preparation can be made of TOPO, DEHPA or trioctylmethylammonium in the detection of acids, metal ions or amino acids or amino acids amino phosphoric acid, respectively (see abstract, Table 1). The Examiner alleged that it would have been obvious to one having ordinary skill in the art at the time the invention was made to use TOPO, DEHPA or trioctylmethylammonium as part of the membrane in the detection of analytes to specifically separate analytes of interest according to ones needs for experimentation.

In response, Applicants respectfully traverse this rejection. First of all, Applicants submit that claim 1 as amended is patentable over the combination of Varian, Inc. and Ho, and therefore the addition of Jonsson cannot render claim 12 unpatentable, since a dependent claim cannot be rendered obvious by adding an additional limitation to a nonobvious independent claim (claim 1). Further, while the Examiner is correct that Jonsson discloses trioctylphosphine oxide (TOPO), diethylhexyl phosphoric acid (DEHPA) and trioctylmethylammonium chloride in Table 1, it does so in the context of their use in a chemical reaction to trap analyte molecules that have passed through the membrane into the acceptor solution, by creating a charged ion that prevents the back-extraction into the membrane, and allegedly creating a driving force for high enrichment of the analyte. See section 2.2 "Three-phase membrane extraction", pages 496-497. Therefore, Jonsson *teaches away* from the use of those agents as carriers as claimed in claim 12.

Docket No.: 03-41US  
Serial No. 10/788,592

In addition, Jonsson teaches the use of these trapping agents in conjunction with organic liquids such as long chain hydrocarbons like n-undecane or kerosene, or more polar compounds like di-hexyl ether or tri-octyl phosphate. There is no teaching, suggestion or motivation in Jonsson or the art to use the cited agents in conjunction with liquid membranes formed from vegetable oils or fatty acid esters, or any assurance that these agents could even act as carriers when used with liquid membranes formed from vegetable oils or fatty acid esters. Therefore, one skilled in the art at the time the invention was made *would not have had a reasonable expectation of success* in using these trapping agents with liquid membranes formed from vegetable oils or fatty acid esters.

Applicants thus respectfully submit that the rejection of claim 12 over Varian, Inc. and Ho as applied to claim 1 above, and further in view of Jonsson, has been overcome and should be withdrawn.

**VII. REJECTIONS UNDER 35 U.S.C. § 103(a) OVER WO 02/0088672 AND U.S. PATENT NO. 5,507,949 AND FURTHER IN VIEW OF U.S. PATENT NO. 4,990,334**

Claim 16 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Varian, Inc. and Ho as applied to claim 1 above, and further in view of U.S. Patent No. 4,990,334 to Admassu (hereinafter "Admassu"). The Examiner stated that Varian, Inc. and Ho discloses the claimed invention. The Examiner conceded that Varian, Inc. does not disclose that the liquid membrane is stable for at least 30, 60 or 90 days. The Examiner stated that Admassu discloses a method for treating liquid-wet polycarbonate membrane to improve separation properties where they are stored in water at ambient or elevated temperature and pressure for a period of time sufficient to provide uniform membrane composition, and that the membranes are preferably stored in water at ambient temperature and pressure for at least 2 hours and more preferably for at least 24 hours, even more preferably for at least 5 days, and most preferably for 10 days (see abstract, column 4, lines 54-61). The Examiner alleged that it would have been obvious to one having ordinary skill in the art at the time the invention was made to store the liquid membranes for at least 30, 60 or 90 days to allow complete formation of the liquid membrane promoting better separation and to store the membranes for future use in different experimentation.

With respect to claim 24, the Examiner conceded that Varian, Inc. does not disclose the liquid membrane is stable for at least 30, 60 or 90 days, and stated that Admassu discloses

Docket No.: 03-41US  
Serial No. 10/788,592

a method for treating liquid-wet polycarbonate membrane to improve separation properties where they are stored in water at ambient or elevated temperature and pressure for a period of time sufficient to provide uniform membrane composition. The Examiner stated that the membranes are preferably stored in water at ambient temperature and pressure for at least 2 hours and more preferably for at least 24 hours, even more preferably for at least 5 days, and most preferably for 10 days (see abstract, column 4, lines 54-61). The Examiner alleged that it would have been obvious to one having ordinary skill in the art at the time the invention was made to store the liquid membranes for at least 30, 60 or 90 days to allow complete formation of the liquid membrane promoting better separation and to store the membranes for future use in different experimentation.

In response, Applicants respectfully traverse these rejections. Admassu purports to disclose a process for treating liquid-wet polycarbonate membranes to reduce the concentration of liquid present in the membrane to below about 1.0 weight percent, or more preferably, below about 0.3 weight percent. The membranes can be optionally stored in water for a time sufficient to provide a uniform membrane composition. See Col. 3, lines 25-35 and Col. 4, lines 54-57. After storage in water, the membranes are dried and heat treated and then used to isolate or recover gases from gaseous mixtures. See Col. 5, line 63 - Col. 7, line 14. Although the Examiner correctly cites Admassu for stating that the membranes may optionally be stored in water for extended periods of time, Applicants point out that these polymeric membranes do not include a liquid membrane at all, and thus the teachings of Admassu are not relevant to the patentability of the pending claims. In other words, the *combination of references does not teach the subject matter of the rejected claims*, and therefore cannot render them obvious.

Further, based on the teachings of Admassu, one skilled in the art at the time the invention was made *would not have had a reasonable expectation of success* that a liquid membrane supported on a porous polymeric substrate could be stable for at least 30 days, 60 days or 90 days. In addition, the instant Specification clearly shows that the liquid membrane is stable for the desired period of time when stored in a container open to the air or closed, but not under water.

Accordingly, Applicants respectfully submit that the rejections of claims 16 and 24 over Varian, Inc. and Ho as applied to claim 1 above, and further in view of Admassu have been overcome and request that the rejections be withdrawn.

**Docket No.: 03-41US  
Serial No. 10/788,592**

**VIII. REJECTIONS UNDER 35 U.S.C. § 103(a) OVER WO 02/0088672 AND U.S. PATENT NO. 5,507,949 AND FURTHER IN VIEW OF U.S. PATENT NO. 5,160,627**

Claim 48 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Varian, Inc. and Ho as applied to claim 2 above, and further in view of U.S. Patent No. 5,160,627 to Cussler et al. (hereinafter "Cussler"). The Examiner stated that Varian, Inc. and Ho disclose the claimed invention except for where the liquid membrane supported on a hollow fiber is stored in a closed container prior to use. The Examiner stated that "Cussler discloses a process for modifying the properties of a hydrophobic microporous member where the pore-filled microporous hollow fiber members are used in a broad range of chromatographic separations applications such as liquid-liquid extractions and the pore-filled hollow fibers constitute stabilized, immobilized liquid membranes having a utility generally where the membranes are needed." The Examiner stated that a module of the hydrophobic microporous member comprises a housing and plurality of hollow fibers (see column 8, lines 22-31, claim 3). The Examiner alleged that it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide a housing for the membranes to be stored in before use to preserve the separation integrity of the membrane and to prevent contamination from the environment and human touch before use.

Regarding claim 49, the Examiner stated that Varian, Inc. and Ho discloses the claimed invention except for where the liquid membrane supported on a hollow fiber is stored in a closed container prior to use. The Examiner stated that "Cussler discloses a process for modifying the properties of a hydrophobic microporous member where the pore-filled microporous hollow fiber members are used in a broad range of chromatographic separations applications such as liquid-liquid extractions and the pore-filled hollow fibers constitute stabilized, immobilized liquid membranes having a utility generally where the membranes are needed." The Examiner stated that a module of the hydrophobic microporous member comprises a housing and plurality of hollow fibers (see column 8, lines 22-31, claim 3). The Examiner alleged that it would have been obvious to one having ordinary skill in the art at the time the invention was made to provide a housing for the membranes to be stored in before use to preserve the separation integrity of the membrane and the prevent contamination from the environment and human touch before use.

In response, Applicants respectfully traverse these rejections. First of all, Applicants

**Docket No.: 03-41US  
Serial No. 10/788,592**

submit that claims 1 and 20 as amended are patentable over the combination of Varian, Inc. and Ho, and therefore the addition of Cussler cannot render claims 48 and 49 unpatentable, since a dependent claim cannot be rendered obvious by adding an additional limitation to a nonobvious independent claim. In addition, Cussler describes polymerizing polyvinyl alcohol and divinyl sulfone in the pores of a hydrophilic microporous membrane and using the membranes in liquid chromatography applications. Again, there is no liquid membrane supported on the membranes so described, and thus Cussler is irrelevant to the patentability of claims 48 and 49. In other words, the *combination of references does not teach the subject matter of the rejected claims*, and therefore cannot render them obvious.

Accordingly, Applicants respectfully submit that the rejections of claims 48 and 49 over Varian, Inc. and Ho as applied to claim 2 above, and further in view of Cussler has been overcome and request that the rejections be withdrawn.

**CONCLUSION**

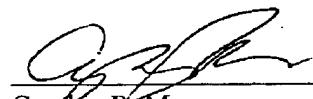
Entry of this Amendment is respectfully requested. Favorable consideration is respectfully requested in view of the foregoing Amendments and Remarks.

If the Examiner has any questions concerning this communication, or would like to discuss the application, the art, or other pertinent matters, she is welcome to contact the undersigned attorney at (650) 565-8185.

As this submission is timely submitted and no additional excess claims fees have been incurred, there are no fees due.

Respectfully submitted,

By:

  
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